

The Examiner's reading of the prior art is set forth in the Action and will not be repeated here except as necessary to an understanding of Applicants' traversal of the rejection, which is now presented.

Claim 10 of the present application basically calls for method for detecting and treating malignant tumors, comprising:

- administering a tumor detecting effective amount of a 5-ALA isotope of a specific type;

- detecting the malignant tumor using NMR; and

- administering an amount of the 5-ALA isotope effective to kill the malignant tumors.

While over simplified, the method of claim 10 can be characterized as involving:

- administering a 5-ALA isotope to detect;

- detecting using NMR; and

- killing using the 5-ALA isotope.

Claim 11 calls for the use in combination with a carrier.

The Examiner interprets Kennedy as teaching the broad concept of detecting malignant tumors using 5-ALA and then subsequent treatment by exposure to photoactivating light using 5-ALA.

The Examiner then turns to Jichlinski, and seems to correctly characterizes the teaching of Jichlinski except as later explained.

It is not clear why the Examiner (page 3 of the Action) states that the use of either a fluorescence label or a radiolabel in the detection scheme of Jichlinski would be obvious to one of ordinary skill in the art.

Kajiware is the first reference that teaches 5-ALA isotopes. Kajiware is specific to the carbon isotope, not the nitrogen isotope. The Examiner views Kajiware as teaching such a 5-ALA isotope for diagnostic purposes. Applicants note the disclosure at page 5 of Kajiware regarding the use of PBG.

The Examiner finally turns to Jaffe as disclosing the use of NMR to detect 5-ALA carbon and nitrogen isotopes. The teaching of Jaffe seems to be that the presence of a 5-ALA molecule (carbon or nitrogen isotope) can be detected by NMR.

The Examiner's ultimate conclusion regarding the combination of references is set forth at page 3 of the Action.

Applicants respectfully submit that based on this record there is no motivation for one of ordinary skill in the art to combine Kennedy with Jichlinski, Kajiware and Jaffe to reach the present invention.

Specifically, Kennedy is directed to an invention, which relates to medical treatment. In Kennedy, ALA is administered to a patient with cancer to preferentially accumulate protoporphyrin IX (Proto IX). Once the ALA is preferentially accumulated, when such cancers as exposed to photoactivating light, the malignant tissue is selectively destroyed by

photodynamic action. It is believed that the above is a fair assessment of the teaching of Kennedy.

In distinction to Kennedy, Kajiwara and Jaffe relate to the biochemical arts, specifically Kajiwara and Jaffe involve the structural analysis of a molecule being carried out using an isotope for metabolic studies. It is believed that this is a fair assessment of the teaching of Kajiwara and Jaffe.

Medical treatment techniques and studies on metabolism by structural analysis relate to quite different technical fields, the problems involved are not the same and the specialized knowledge involved in the medical treatment field and in the study of metabolism by structural analysis are quite different and bear little, if any, relationship to each other.

Accordingly, it is respectfully submitted that one of ordinary skill in the art dealing with medical treatments would not be motivated nor would such individual sufficiently understand metabolic studies based on structural analysis to be motivated to modify Kennedy in view of Kajiwara and/or Jaffe. In a similar fashion, it is respectfully submitted that one of ordinary skill in the art of metabolic studies based on structural analysis would not sufficiently understand the medical treatment art and the unique problems involved in the medical treatment art to be motivated to modify Kennedy in view of Kajiwara and/or Jaffe.

It must be kept in mind that the present invention is directed to a method for detecting and treating malignant tumors. It is not *per se* directed to metabolic studies based on structural analysis. The Examiner is respectfully requested to address the issue as to why one of ordinary skill in the art of medical treatment would be motivated to turn to the art of metabolic studies

based on structural analysis for any problem which would be encountered in the medical treatment arts. Clearly *per se* the two areas of medical treatment and metabolic studies based on structural analysis are not the same art.

In Kajiwara and Jaffe isotope labeled ALA is administered to a subject and subjected to a biochemical reaction. Following the teaching of Kajiwara and Jaffe, an objective compound is separated and purified, a position in the molecule has introduced thereto an isotope and examination is conducted by NMR analysis. Metabolic results are predicted or expected based on the results of the NMR analysis. Neither reference has any relationship to medical treatment as in Kennedy or as in the present invention.

*their invention*  
In distinction, in accordance with the present invention, isotope labeled ALA is administered to the living body (a subject) and subjected therein to a biochemical reaction. Malignant tumors are then detected by the distribution of the isotope in the living body of the subject without any separation of the compound.

Assuming, *arguendo*, Kennedy were to be combined with Kajiwara and/or Jaffe, to one of ordinary skill in the art the teaching of the combination of references would be that a compound such as Proto IX or porphobilinogen (PBG) could be separated and purified from malignant tumors and, possibly, though this is not very clear from Kajiwara or Jaffe and is in a sense a hindsight view, one of ordinary skill in the art might conclude that metabolic disorders in a malignant tumor could be examined. However, one of ordinary skill in the medical arts or one of ordinary skill in the art of metabolic studies by structural analysis (the test would apply both ways) would not be reasonably motivated to expect a reasonable chance of success that the

amount of the isotope label could be measured in a living body and that the result could be applied to medical techniques as at issue in the present claims.

In Kennedy, light exposure is essential for the detection of malignant tumors, and "wet" operations such as incision or endoscope insertion are necessary. In distinction, in accordance with the present invention, diagnosis can be carried out by what might be considered "low-wet" operations involving a combination of an isotope and NMR or MRI.

In summary, one of ordinary skill in the art would not reasonably be able to predict or expect the present invention disclosing diagnosis in which isotope labeled ALA is administered and the position of malignant tumors is determined or searched by examining the position of the isotope label in a living body, without separating the isotope-label ALA.

Kajiware does disclose that PBG, which is produced, is useful as a therapeutic drug for lead poisoning. In the Kajiware diagnosis,  $^{13}\text{C}$ -label PBG is administered, a metabolized compound is separated and purified, and the structure of the metabolized compound is detected using NMR. Thus, at best, a disruption in enzymatic reactions can be detected in accordance with the teachings of Kajiware. The Kajiware technique is based on the principle that an enzyme, specifically ALA dehydratase, which metabolizes ALA to PBG, is inactivated by lead. Quite clearly, the teaching or technique in Kajiware is simply an extension involving biochemical studies of metabolic reactions using structural analysis.

Equally as clearly, it is respectfully submitted that the present invention wherein malignant tissue is detected from a position where an isotope is accumulated in a living body is quite different from Kajiware in principle and in basic concept.

In Jaffe, in order to analyze the function of the enzyme ALA dehydratase, which condenses ALA to produce PBG, the interaction between isotope-label ALA and the enzyme was examined. Jaffe thus simply relates to analyzing a reaction mechanism, which is quite different from any procedure or concept in accordance with the present invention.

Applicants thus respectfully submit that the present invention, where malignant tissue is detected from a position where an isotope is accumulated in the living body and is then killed using the 5-ALA isotope, is quite different from Jaffe which simply examines the interaction between isotope-label ALA and an enzyme.

Since both Kajiwara and Jaffe are essential to support or perfect the rejection which the Examiner has posed, Applicants believe that the rejection is improper based on the above analysis and request withdrawal.

However, Applicants now turn to Jichlinski, which the Examiner may consider the reference which "links" Kennedy with Kajiwara/Jaffe. Applicants respectfully submit that Jichlinski does not provide any teaching over that of Kennedy which would motivate one of ordinary skill in the art to use the materials of Kajiwara or Jaffe in the Kennedy procedure.

Specifically, as is the case with Kennedy, Jichlinski simply deals with 5-ALA. Although in the ABSTRACT Jichlinski refers to the Jichlinski method as being very helpful "in finding and treating any residual malignant spots at the end of the transurethral bladder resection.", quite clearly Jichlinski in no fashion contemplates that the isotopes of 5-ALA used in accordance with the present invention would exhibit the function of killing tumors, as called for in claim 10 of the

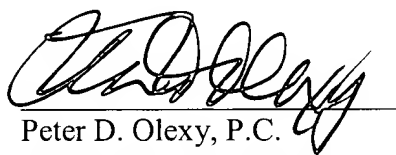
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present application. Further, of course, Kennedy, Kajiwara and Jaffe are all silent on this aspect of the present invention.

Thus, Applicants respectfully submit there is no motivation to combine Kennedy and/or Jichlinski with Kajiwara and/or Jaffe, and there is no teaching of the subject matter of claim 10 as claimed.

Withdrawal of the rejection is requested.

Respectfully submitted,

  
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